Oral Presentations

ALLOGENEIC TRANSPLANTS

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BRONCHIOLITIS OBLITERANS SYNDROME FOLLOWING ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: PREVALENCE, RISK FACTORS, AND OUTCOMES

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We conducted a retrospective cohort study of the prevalence, risk factors and outcomes of bronchiolitis obliterans syndrome (BOS), a serious late pulmonary complication of allogeneic hematopoietic cell transplantation (aHCT).

Methods: Pulmonary function tests (PFTs) from 1145 patients who received their first aHCT between January 1, 2002 and June 30, 2006 were screened at ≥ 1 year after aHCT to identify patients who met the NIH spirometry criteria for BOS (FEV1 ≤ 75% and FEV1/VC ratio < 0.7) and had a ≥ 10% decline in FEV1 compared to pre-transplant values. Clinical, microbiologic, and radiologic records were reviewed to exclude pulmonary infection and other causes of air-flow obstruction as well as record supportive evidence for BOS.

Results: The overall prevalence of BOS among all transplanted patients was 5.5%. The prevalence of BOS among patients with chronic graft-versus-host disease (cGVHD) and patients surviving to at least 1 year were 16% and 10%, respectively. The median time from transplant to meeting spirometric criteria for BOS was 439 days (range 274-1690). 60% of the 63 total cases were clinically recognized at the time of meeting NIH criteria, 23% were recognized after meeting NIH criteria, and 17% were never clinically recognized. At the time of meeting NIH spirometric criteria, 95% of cases had concurrent evidence of air trapping on PFTs (n = 58) and/or supportive evidence of BOS on high-resolution chest CT (n = 25). BOS was significantly associated with cGVHD ($p < 0.001$), low baseline FEV1 ($p = 0.035$), and low baseline FEV1/VC ratio ($p = 0.001$), but not with other previously identified risk factors such as busulfan-based regimen, peripheral blood stem cell source, donor-recipient gender mismatch, or acute GVHD. 48% of BOS patients were on an immune taper within 3 months prior to meeting NIH criteria. Survival analysis revealed a significant difference in Kaplan Meier survival estimates between subjects with and without BOS ($p = 0.002$). Non-relapse survival differed significantly based on clinical recognition status at the time of meeting spirometric criteria ($p = 0.027$), with concurrently-recognized patients having the worst survival.

Conclusion: These results suggest that BOS may be more prevalent than previously thought. Frequent assessment of high-risk patients with cGVHD may help with earlier detection and intervention for this often-fatal disease.

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PROSPECTIVE COMPARISON OF REDUCED INTENSITY (FLU-BU-ATG) VS. NON-MYELOABLATIVE (FLU-TBI) CONDITIONING FOR MATCHED RELATED ALLO-SCT: A CLINICAL AND COST-EFFECTIVENESS MULTICENTER ITAC STUDY (MINI VS. MICRO TRIAL)

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We prospectively compare 2 RIC: FBA (Fluda (150 mg/m^2)+Oral Bu (8 mg/kg) + Thymoglobuline (2.5 mg/kg)) (IS: CSA) or FTBI (Fluda (90 mg/m^2)+2 Gy TBI) (IS: CSA + MMF). Inclusion criteria: hematological malignancies, pts non eligible for myeloablative CDT, age between 18 and 65, HLA identical sibling. Groups (FBA: N = 69; FTBI: N = 70) were comparable: age 54 (21-65); Male: 65%; Diag: AL 18%; NHL 23%; MM 39% others 20%; status: CR: 32%; SD = 60%; REF = 8%). Graft failure occured in 4 pts (6%) in FTBI. Cumulative incidences (CI) of grade >= 2 aGVHD and cGVHD were respectively: 37% (FBA 51%; FTBI 26%; $p = .003$) and 77% (FBA 79%; FTBI 76%: p = NS). At 1 year, PFS differed (FBA 0.68 [0.56 – 0.78]; FTBI 0.51 [0.39 – 0.62]; $p = 0.048$) while OS was similar (FBA 0.75 [0.63 – 0.84]; FTBI 0.74 [0.62 – 0.83]; p = NS). With a f.up of 39 months (3-71), 72 pts were alive (FBA: 35; FTBI: 37: p = NS) for a 5 year probability of 0.45 [0.31– 0.57] and 0.49 [0.35– 0.61] for FBA and FTBI respectively (p = NS). 5 year PFS probability were 0.35 [0.22– 0.48] for FBA and 0.23 [0.10–0.38] for FTBI (p = NS). Median PFS were 26.3 (IC95%:13.6 – 47.3) and 13.1 (IC95%:7.4 – 25.6) months (mths) in FBA and FTBI respectively. More relapses/progressions occurred in FTBI ($p = .005$): 5 year relapse/progression CI of 0.28 [0.16– 0.40] (FBA) and 0.50 [0.39–0.60] (FTBI). 3 pts died from secondary cancers (FBA: 1; FTBI: 2) and 38 from TRM with a 5 year TRM CI of 0.37 [0.25– 0.49] for FBA and 0.24 [0.14– 0.34] for FTBI (p = 0.199). FBA had a stronger negative impact on patients' QOL up to 80 days and resolved (EORTC QLQ-C30 questionnaire). Evaluation of medical direct costs demonstrated a crude advantage for FTBI (66,711€ vs 42,080€ for the FBA and FTBI respectively, $p < 0.001$). The cost-effectiveness ratio using PFS as endpoint was 22,392 € per year of life free of relapse gained using FBA conditioning regimen when compared to FTBI. In conclusion, these 2 regimens produce similar 1 year OS. However, FBA is associated with better 1 year PFS and socially acceptable cost-effectiveness ratio but worse early QOL. FBA is also associated with better long term disease control, whereas FTBI tends to produce lower TRM and higher rejection rates.

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TNF-INHIBITION WITH ETANERCEPT FOR GVHD PREVENTION IN ALTERNATIVE DONOR HCT: LOWER TNFR1 LEVELS CORRELATE WITH BETTER OUTCOMES

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TNF Receptor 1 (TNFR1) levels have previously been shown to predict GVHD, non-relapse mortality (NRM) and overall survival. We therefore conducted a phase II trial at two centers between 2005 and 2009 using the TNF-inhibitor etanercept together with standard tacrolimus/methotrexate in high-risk allogeneic matched unrelated donor (URD) (n = 68), single antigen mismatched URD (n = 25), or single antigen mismatched related donor (n = 3) hematopoietic cell transplant (HCT) recipients. The median age was 45y (range 2-61y). Patients received etanercept (0.4 mg/kg, max 25 mg) twice weekly from the start of conditioning to day 56 in addition to tacrolimus and methotrexate (5 mg/m^2 on days 1, 3, 6, and 11). The myeloablative conditioning regimens included fludarabine and IV busulfan 12.8 mg/kg (FluBu4, n = 31), BCNU/etoposide/cyclophosphamide or busulfan/cyclophosphamide (BCNU/Busulfan, n = 36), and TBI/cyclophosphamide (TBI, n = 29).

We hypothesized that the administration of the TNF-inhibitor etanercept would lower TNFR1 levels, and thereby protect against GVHD and NRM while improving survival. The median day 7 TNFR1 level was 2518 pg/mL in study patients, significantly lower than the 3529 pg/mL seen in 132 control patients ($p < 0.001$) matched for age, conditioning regimen, degree of HLA-match, and disease status. We then examined whether day 7 TNFR1 levels were associated with outcomes in study patients and found an increased risk for NRM (HR 2.0, $p < 0.001$) and death (HR 1.5, $p < 0.06$) for each doubling of TNFR1 levels. As shown in the Table, the day 7 TNFR1 levels differed statistically according to the myeloablative conditioning regimen ($p < 0.001$). FluBu4 patients experienced the lowest day 7 TNFR1 levels compared to other study patients and had the lowest rates of grade 2-4 GVHD (39% $p = 0.04$), no deaths in the